Cognitive behaviour therapy for the chronic fatigue syndrome: a randomised controlled trial

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Abstract

***Objective*—To evaluate the acceptability and efficacy of adding cognitive behaviour therapy to the medical care of patients presenting with the chronic fatigue syndrome.**

***Design*—Randomised controlled trial with final assessment at 12 months.**

***Setting*—An infectious diseases outpatient clinic.**

***Subjects*—60 consecutively referred patients meeting consensus criteria for the chronic fatigue syndrome.**

***Interventions*—Medical care comprised assessment, advice, and follow up in general practice. Patients who received cognitive behaviour therapy were offered 16 individual weekly sessions in addition to their medical care.**

***Main outcome measures*—The proportions of patients (*a*) who achieved normal daily functioning (Karnofsky score 80 or more) and (*b*) who achieved a clinically significant improvement in functioning (change in Karnofsky score 10 points or more) by 12 months after randomisation.**

***Results*—Only two eligible patients refused to participate. All randomised patients completed treatment. An intention to treat analysis showed that 73% (22/30) of recipients of cognitive behaviour therapy achieved a satisfactory outcome as compared with 27% (8/30) of patients who were given only medical care (difference 47 percentage points; 95% confidence interval 24 to 69). Similar differences were observed in subsidiary outcome measures. The improvement in disability among patients given cognitive behaviour therapy continued after completion of therapy. Illness beliefs and coping behaviour previously associated with a poor outcome changed more with cognitive behaviour therapy than with medical care alone.**

***Conclusion*—Adding cognitive behaviour therapy to the medical care of patients with the chronic fatigue syndrome is acceptable to patients and leads to a sustained reduction in functional impairment.**

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Introduction

The chronic fatigue syndrome is characterised by a principal complaint of severe fatigue of at least six months' duration associated with appreciable disability and unexplained by recognised organic disease.[1-4] Various causes have been proposed, including chronic viral infection, dysfunction of the immune system, neuroendocrine disturbance, and depression, but all remain controversial.[5,6] Many pharmacological treatments have been suggested, but none are of proved value.[7]

Cognitive behaviour therapy offers a novel approach to treatment of the chronic fatigue syndrome. It is based on the hypothesis that inaccurate and unhelpful beliefs, ineffective coping behaviour, negative mood states, social problems, and pathophysiological processes all interact to perpetuate the illness.[8,9] Treatment aims at helping patients to re-evaluate their understanding of the illness and to adopt more effective coping behaviours.[7-9] An early uncontrolled evaluation of this type of treatment produced promising results in many patients but was unacceptable to some.[10] Two subsequent controlled trials found cognitive behaviour therapy to offer no benefit over non-specific management.[11,12] However, the form of cognitive behaviour therapy evaluated may have been inadequate. In particular, previously evaluated forms may have failed to address effectively the illness beliefs and coping behaviours known to predict treatment compliance and outcome.[10,13,14]

We have developed a form of cognitive behaviour therapy specifically for patients with chronic fatigue and related syndromes which includes a collaborative re-evaluation of patients' beliefs about the illness.[15,16] We wanted to find out if adding this form of cognitive behaviour therapy to basic medical care would be acceptable to patients and improve their daily functioning. We also wanted to know if it would result in greater changes in illness beliefs and coping behaviour.

Patients and methods

The study was conducted at the John Radcliffe and Warneford Hospitals in Oxford. The protocol was approved by the local ethics committee.

Patients were recruited from consecutive referrals to a hospital infectious diseases outpatient clinic. All patients aged 18-60 with a major complaint of fatigue were medically assessed by a consultant physician (DW or TP). Those whose symptoms were unexplained by organic disease were reinterviewed by one of us (MS) and a full history and psychiatric diagnostic interview[17] completed to determine eligibility for inclusion.

The inclusion criteria specified that patients had to meet the "Oxford" criteria for the chronic fatigue syndrome.[3] Specifically they had to have (*a*) a principal complaint of fatigue exacerbated by physical or mental activity, or both, of six months' duration; (*b*) impairment of daily activities (Karnofsky score <80; see below); and (*c*) no clinically significant findings on physical examination or laboratory investigation (full blood count, C reactive protein concentration, biochemical measurements, and thyroxine and thyroid stimulating hormone concentrations).

Patients were excluded if they (*a*) were currently receiving psychotherapy or antidepressant drugs (unless they had been taking the same dose for at least three months without improvement); (*b*) were unwilling to accept randomisation or were unavailable for follow up; (*c*) met criteria for severe depression (melancholia) or had a history of bipolar affective disorder, schizophrenia, or substance misuse (as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R)[18]); or (*d*) were at significant risk of suicide or in need of urgent psychiatric treatment.

The required sample size of 60 patients was estimated with the assumption of (*a*) clinically significant improvement in 20% of the patients who received medical care[13] and 60% who also received cognitive behaviour therapy,[10] (*b*) a low drop out rate, and (*c*) a significance level of 5% and a power of 80%.

DESIGN

The study was a randomised controlled trial in which medical care alone was compared with medical care plus cognitive behaviour therapy. The principal outcome measure was the percentage of patients meeting prespecified outcome criteria. Subsidiary outcome measures and evaluations were included to allow description of the time course and pattern of recovery (see below).

RANDOMISATION

Immediately after assessment eligible patients were randomly allocated to one of the two treatment conditions by means of a sequence of labelled cards contained in sealed numbered envelopes. The allocation sequence was based on a random number table and was both restricted (blocks of four, balanced to obtain equal numbers in each treatment condition) and stratified for the presence of major depressive disorder.[18]

TREATMENT CONDITIONS

Medical care alone—Patients randomised to receive medical care alone were reassured that there was no evidence of serious organic disease, told that they had the chronic fatigue syndrome, and advised to increase their level of activity by as much as they felt able. No further specific explanation or advice was given. Patients were followed up by their general practitioners in the usual way.

Medical care plus cognitive behaviour therapy—In addition to the medical care outlined above, patients given cognitive behaviour therapy were invited to attend 16 one hour individual treatment sessions over four months. The treatment had a cognitive emphasis[19] and was tailored for patients with the chronic fatigue syndrome.[15,16] It was administered by three experienced therapists (CS, IK, MS). Therapy was codified in a manual and supervised by an experienced cognitive therapist (AH). During treatment patients were encouraged to question a simple disease explanation of the illness and to consider the role of psychological and social factors. They were also invited to evaluate the effect of gradual and consistent increases in activity and to try strategies other than avoidance. Additional components of the treatment included strategies to reduce excessive perfectionism and self criticism and an active problem solving approach to interpersonal and occupational difficulties.

PATIENT EVALUATIONS

Patient evaluations comprised both a semistructured interview and patient rated questionnaires. All were conducted by the same assessor (SS). Evaluations took place before randomisation, after the initial treatment period (five months), at eight months, and, finally, at 12 months after entry.

Patient functioning was assessed in several ways. The principal measure was based on interviewing the patient about his or her activities over the previous month (corroborated by a cohabitee when possible). A summary of the findings was subsequently rated on the Karnofsky scale[20] by another researcher, who was blind to the patient's treatment. We defined two clinically relevant end points: (*a*) the achievement of a score of 80 or more (normal functioning); (*b*) an improvement of 10 points or more (clinically significant change). The Karnofsky scale was reportedly valid and reliable in several patient populations.[21] In this study good agreement was observed between two raters in the allocation of patients to the specified outcome categories (Cohen's κ greater than 0·8 at every time point).[22] Subsidiary measures of functioning included a patient rating of interference with daily activities,[23] improvement in employment status, and number of days spent in bed each week. A timed walking test was also included. The patient was asked to walk as quickly as possible along a 20 metre corridor for six minutes and the distance covered recorded.[24] This measure had good test-retest reliability (intraclass correlation 0·97)[22] when repeated one week later in a subsample of 16 patients.

Symptoms were assessed on patient rated scales. Fatigue was measured on a Likert-type scale scored from zero to 10 and depression and anxiety on the hospital anxiety and depression scale.[25]

Overall change was assessed on a seven point patient rated scale ("very much improved" to "very much worse").

Illness beliefs and coping behaviours were also assessed as process measures. Strength of beliefs about the illness was measured on patient rated seven point Likert-type scales ("totally agree" to "totally disagree") and frequency of coping behaviours (for example, avoiding exercise) on five point patient rated scales ("never" to "all the time"). Patients also indicated their view of the nature of the illness on a five point scale ("entirely physical" to "entirely psychological").[26]

STATISTICAL ANALYSIS

The analysis was based on intention to treat and all patients were included. The relative effectiveness of the two treatment conditions was determined by comparing the percentage of patients meeting the predetermined outcome criteria and the significance of the difference assessed by χ^2 test. Significance testing was restricted to these comparisons to avoid the problems of interpretation associated with multiple testing.

Subsidiary measures and other time points were included to describe the nature and pattern of change. The mean change in each from baseline and the difference between the groups in the amount of change were calculated with 95% confidence intervals (unadjusted for multiple significance testing).

The percentage of patients reporting a reduction in those illness beliefs and coping behaviours previously found to be associated with poor outcome (strong belief in a physical cause or persistent viral infection and extreme avoidance of exercise)[10,13,14] between baseline and the end of treatment was calculated in each treatment group and the significance of the difference determined by χ^2 test.

Results

One hundred and twenty three patients were assessed for eligibility. Forty nine did not meet study criteria for the chronic fatigue syndrome. Twelve others were excluded for other reasons—severe depression (five), bipolar disorder (one), active psychiatric treatment (three), unavailability for follow up (three). Only two eligible patients refused, and 60 were recruited into the study. The patients' baseline characteristics are shown in tables 1 and 2. The treatment groups did not differ substantially in age, sex, educational level, marital status, functional impairment on the Karnofsky scale, or psychiatric diagnoses. However, patients in the cognitive behaviour therapy group spent more days in bed, and fewer of them were actively employed. All patients fulfilled recently revised criteria for the chronic fatigue syndrome.[4]

COMPLIANCE AND CONCURRENT INTERVENTIONS

All the patients offered cognitive behaviour therapy accepted and completed the treatment. Eight patients (six in the cognitive behaviour therapy group, two in the standard care group) were taking low dose antidepressants at entry. The mean numbers of visits to general practitioners and the proportions of patients

Table 1—*Demographic and clinical characteristics of treatment groups at baseline*

	Cognitive behavioural therapy (n=30)	Medical care (n=30)
Patient characteristics		
Mean (SD) age (years)	34 (9·1)	38 (11·8)
Men:women	12:18	7:23
Married or cohabiting (% (No))	63 (19)	47 (14)
Education after 18 years (% (No))	50 (15)	73 (22)
Not working or studying (% (No))	87 (26)	50 (15)
Member of patient group (% (No))	40 (12)	43 (13)
Illness characteristics		
Reported "infection" at onset (% (No))	67 (20)	73 (22)
Duration of illness in months:		
Median (range)	17 (6-91)	20 (6-86)
Mean (SD)	33·6 (9·1)	29·7 (24·1)
Disability on Karnofsky scale:		
Median (range)	72 (60-78)	72 (65-78)
Mean (SD)	71 (3·3)	72 (3·4)
Psychiatric diagnoses (DSM-III-R)†		
Major depressive disorder (% (No))	20 (6)	20 (6)
Any depressive disorder (% (No))‡	53 (16)	57 (17)
Any anxiety disorder (% (No))§	47 (14)	50 (15)
Any anxiety or depression diagnosis	67 (20)	67 (20)
Somatisation disorder	10 (3)	10 (3)

†Patients may have more than one diagnosis.
‡Major depression, dysthymia, and depression not otherwise specified.
§Generalised anxiety disorder, panic, agoraphobia, social phobia, and anxiety not otherwise specified.

Table 2—*Subsidiary variables in each treatment group at baseline*

	Cognitive behavioural therapy (n=30)	Medical care (n=30)
Mean functioning (SD)		
Percentage interference with activities	65 (13)	64 (15)
No of days in bed each week	3·3 (2·0)	1·6 (1·5)
Distance walked in 6 minutes (m)	424 (103)	435 (140)
Mean symptom severity (SD)		
Fatigue severity (0-10 scale)	7·8 (1·5)	7·9 (1·9)
Depression (hospital anxiety and depression scale)	6·7 (3·6)	6·8 (3·6)
Anxiety (hospital anxiety and depression scale)	6·3 (3·5)	8·4 (5·0)
Illness beliefs and behaviours (% (No))		
Illness is mainly physical†	83 (25)	73 (22)
Cause is a virus‡	67 (20)	63 (19)
Illness is "ME"‡	63 (19)	77 (23)
Avoidance of exercise§	97 (29)	83 (25)

†On five point scale from entirely physical to entirely psychological.
‡Agree with statement. (ME=Myalgic encephalomyelitis.)
§Occurs at least 50% of time.

consulting alternative and complementary practitioners did not differ between the groups during the study. Of those patients allocated to medical care alone, two were referred to psychiatry services and received supportive psychotherapy; one was diagnosed as suffering from coeliac disease and began a gluten free diet; and one received behavioural psychotherapy and full dose antidepressants. Of those patients allocated to additional cognitive behaviour therapy, one received counselling as part of vocational retraining.

COMPLETENESS OF FOLLOW UP AND MISSING DATA

Complete data were obtained for all patients except one, who did not attend the 12 month follow up. As a telephone call to this patient indicated no substantial change since the previous evaluation, these data were used for both. Seven other patients (four in the standard care group, three in the cognitive behaviour therapy group) refused to do the walking test on one or more occasions. In these cases the previous test result was used (reanalyses substituting instead these patients' best and worst distances had little effect on group means).

RESPONSE TO TREATMENT

At the final 12 month assessment the percentage of patients who had attained normal functioning (score 80 or more) on the Karnofsky scale was significantly greater in the group who had received cognitive behaviour therapy ($\chi^2=11·3$, df=1; $P<0·001$). The percentage with an improvement of at least 10 points on the scale was also significantly greater in this group ($\chi^2=13·1$, df=1; $P<0·001$). Group differences and 95% confidence intervals are shown in table 3. Interestingly, the difference between the treatment groups on these measures at five months was small and non-significant but widened progressively during follow up. The greater improvement in the cognitive behaviour therapy group was underscored by the 63% (19/30) of patients in this group who improved in work status as compared with 20% (6/30) of those who received only medical care.

The mean changes in patients' scores on each of the subsidiary outcome measures and the differences in the change between the treatment groups are shown in table 4. Improvements in the patients' perceptions of interference with daily activities, severity of fatigue, performance on the walking test, and reduction in the numbers of days spent in bed were all greater in the patients given cognitive behaviour therapy. Depression but not anxiety improved more with cognitive behaviour therapy.

At the final assessment significant subjective improvement ("much improved" or "very much improved") was reported by 60% (18/30) of the patients who received cognitive behaviour therapy and 23% (7/30) of the patients who had only medical care. Deterioration ("worse" or "much worse") was reported by 13% (4/30) of the cognitive behaviour therapy group and 10% (3/30) of the medical care only group. Two patients given cognitive behaviour therapy attributed their deterioration to the treatment and two experienced only temporary benefit.

CHANGE IN BELIEFS AND COPING BEHAVIOUR

The proportion of patients who reported a reduction in those illness beliefs and behaviours previously

Table 3—*Principal outcome measures, expressed in percentages attaining satisfactory outcome, or improvement*

Time from randomisation (months)	Percentage (No) of patients improved: Cognitive behavioural therapy (n=30)	Percentage (No) of patients improved: Medical care (n=30)	Difference in percentage (95% confidence interval)
Satisfactory outcome on Karnofsky scale†			
5	27 (8)	20 (6)	7 (−15 to 28)
8	53 (16)	30 (9)	23 (0 to 48)
12	73 (22)	27 (8)	47 (24 to 69)
Improvement on Karnofsky scale‡			
5	23 (7)	7 (2)	17 (0 to 34)
8	60 (18)	20 (6)	40 (17 to 63)
12	73 (22)	23 (7)	50 (28 to 72)

†Achieved final score of 80 or more.
‡Improvement from baseline of 10 points or more.

Table 4—*Subsidiary outcome measures, expressed as means and mean change scores*

Time from randomisation (months)	Means: Cognitive behavioural therapy	Means: Medical care	Mean change in scores: Cognitive behavioural therapy	Mean change in scores: Medical care	Difference (95% confidence interval)
Percentage interference with activities					
Baseline	65	64			
5	41	51	−24	−13	11 (1 to 21)
8	39	50	−26	−14	12 (2 to 22)
12	37	50	−28	−14	14 (3 to 25)
No of days in bed per week					
Baseline	3·3	1·6			
5	1·8	1·5	−1·5	−0·1	1·4 (0·3 to 2·5)
8	1·8	1·6	−1·5	0	1·5 (0·3 to 2·8)
12	0·9	2·0	−2·4	0·5	2·8 (1·7 to 4·0)
Distance walked in 6 minutes (m)†					
Baseline	424	435			
5	467	436	43	1	42 (8 to 76)
8	476	436	52	1	51 (14 to 88)
12	481	437	57	2	55 (17 to 94)
Fatigue severity (0-10)					
Baseline	7·8	7·9			
5	5·2	6·6	−2·7	−1·3	1·4 (0·0 to 2·7)
8	4·7	6·4	−3·1	−1·5	1·6 (0·2 to 3·0)
12	4·3	6·3	−3·5	−1·6	1·9 (0·5 to 3·3)
Anxiety (hospital anxiety and depression scale)					
Baseline	6·3	8·4			
5	4·0	6·6	−2·3	−1·8	0·6 (−1·1 to 2·2)
8	4·5	6·5	−1·8	−1·9	−0·1 (−2·0 to 1·8)
12	4·4	6·8	−1·9	−1·6	0·3 (−1·6 to 2·2)
Depression (hospital anxiety and depression scale)					
Baseline	6·7	6·8			
5	4·1	6·0	−2·6	−0·9	1·7 (−0·1 to 3·6)
8	3·9	6·5	−2·8	−0·3	2·4 (0·7 to 4·2)
12	3·6	5·8	−3·1	−1·0	2·0 (0·0 to 4·1)

†Includes some estimated values. See text.

Table 5—*Percentage (number) of patients reporting reduction in strength of illness beliefs and frequency of avoidance between baseline and at end of treatment*

	Cognitive behavioural therapy (n=30)	Medical care (n=30)	χ^2
Illness is mainly physical	33 (10)	7 (2)	5·1*
Cause is a virus	48 (14)†	20 (6)	4·1*
Illness is "ME"	17 (5)	27 (8)	0·2
Avoidance of exercise	60 (18)	30 (9)	4·3*

*P<0·05 (χ^2 test; df=1).
†n=29.

associated with poor outcome was significantly greater in the group who received cognitive behaviour therapy (table 5). These observations support the hypothesis that the cognitive behaviour therapy was effective because of a specific effect on illness perpetuating beliefs and coping behaviour.

Discussion

In this trial cognitive behaviour therapy was both acceptable and more effective than medical care alone in improving patients' day to day functioning in the medium term (though not in the short term). It was also more effective in helping patients to feel better. Though the overall treatment effect was substantial, few patients reported complete resolution of symptoms and not all improved. Predictors of response to cognitive behaviour therapy will be the subject of a separate report.

The difference between the treatment groups at the final assessment was clinically important. Not only was the end point on the principal measure (Karnofsky score) predetermined for its clinical significance but similar clinically relevant changes were found on other objective and self rated measures. This difference can also confidently be attributed to the cognitive behaviour therapy, as randomisation achieved well balanced groups at baseline, all patients were included in the analysis, and there were no measurable differences between the groups in the other treatments received. Furthermore, the specificity of the treatment effect was supported by the observation that relevant illness beliefs and coping behaviour changed more in the patients given cognitive behaviour therapy.

The results are likely to be generalisable to many other patients with the chronic fatigue syndrome. The patients in this study were more functionally impaired than many patients seen in primary care[27] and less chronically ill than many patients attending specialist tertiary referral clinics.[12,14] Nevertheless, we believe that they were typical of patients referred to hospital outpatient clinics.[13]

The improvement in day to day functioning in the group who received cognitive behaviour therapy continued after treatment had ended. Such a long term effect of cognitive behaviour therapy is consistent with its aim of teaching patients to help themselves and has been observed with depression[28] and with the chronic fatigue syndrome.[29] An increasing effect of treatment after it has been completed is a more unusual finding but has been reported in the treatment of chronic back pain.[30]

The effectiveness of cognitive behaviour therapy in this study was similar to that observed in patients who accepted treatment in the initial uncontrolled evaluation.[10] The results differed, however, from those of the two previous controlled trials of cognitive behaviour therapy, one of which was a non-randomised comparison with a waiting list[11] and the other a randomised comparison with basic medical care.[12] The possible reasons for the greater effectiveness of cognitive behaviour therapy in our study include differences in the characteristics of the patients, longer follow up, and possibly less active medical care. However, we think that the main reason that the therapy used in this study was both acceptable to patients and effective was its emphasis on re-evaluating patients' illness beliefs by means of a collaborative rather than an adversarial approach.[15,19]

Though the results tell us little about the aetiology of the chronic fatigue syndrome, they show that a return to normal functioning (albeit often with continuing fatigue) is possible in most cases. Plainly further

Key messages

- The chronic fatigue syndrome is a clinical syndrome characterised by disabling fatigue of uncertain cause
- There is no generally accepted form of treatment
- New findings show that patients referred to hospital for the chronic fatigue syndrome have a better outcome if they are given a course of cognitive behaviour therapy than if they receive only basic medical care
- Clinical improvement with cognitive behaviour therapy may be slow but often continues after treatment has ended
- Cognitive behaviour therapy should be considered as an option for patients presenting with the chronic fatigue syndrome

evaluations of cognitive behaviour therapy are desirable, including comparisons with treatments other than basic medical care. Nevertheless, we believe that our results have potentially important implications for the management of patients presenting to medical clinics with chronic disabling fatigue.

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Relation between plasma lactate and blood cyanide concentrations in acute cyanide poisoning

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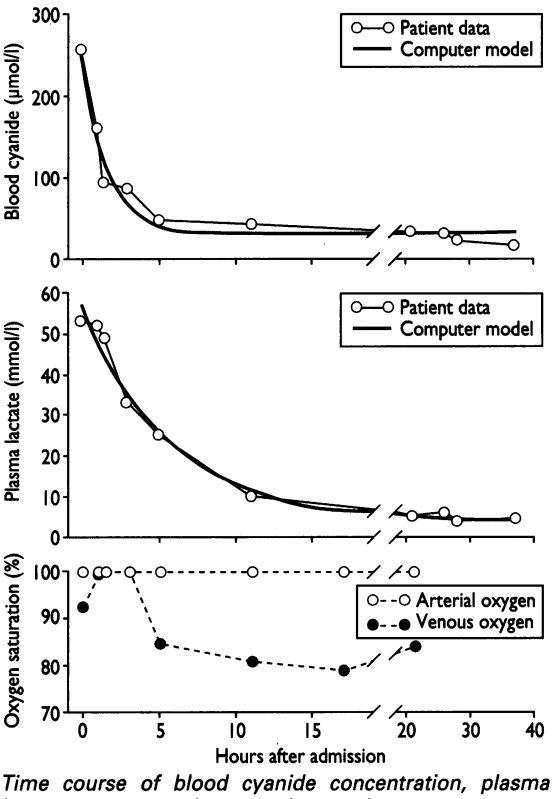
Cyanide poisoning produces rapid blockade of cellular respiration due to binding to cytochrome$_{aa3}$, resulting in accumulation of lactate. Lactic acidosis is a recognised hallmark of acute cyanide poisoning in humans.[1,2] The time course of lactic acidosis, however, has not been well described in relation to evolving blood cyanide concentrations. We studied the relation of blood cyanide to plasma lactate concentrations in a patient with pure acute cyanide poisoning.

Case report

A 63 year old man called for help immediately after suicidal ingestion of a single potassium cyanide capsule. He was conscious on arrival of ambulance staff, but apnoea rapidly supervened, followed by cardiac arrest. Cardiopulmonary resuscitation, endotracheal intubation with 100% pure oxygen, and advanced life support were started. He regained a pulse, with response to painful stimuli.

On arrival at hospital the patient was completely unresponsive and severely hypotensive, with a systolic blood pressure of 35 mm Hg measured by indwelling catheter; his heart rate was 72 beats/minute. Arterial blood gas tensions showed severe metabolic acidosis: pH 7·15, arterial carbon dioxide pressure 24 mm Hg, and arterial oxygen pressure 447 mm Hg; bicarbonate ion concentration 8·2 mmol/l. Gastric lavage and a single dose of activated charcoal were given immediately after the first blood samples were drawn. Intravenous fluids were given and intravenous adrena-



Time course of blood cyanide concentration, plasma lactate concentration, and arteriovenous oxygen saturation in a case of pure cyanide poisoning